PATENT
ATTORNEY DOCKET NO. 08100/003003

Certificate of Mailing: Date of Deposit: 10/14/03

I hereby certify under 37 C.F.R. § 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Colleen Coyne
Printed name of person mailing correspondence

Colleen Coyne
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Brian Seed et al.	Art Unit:	1617
Serial No.:	09/735,024	Examiner:	S. Hui
Filed:	December 12, 2000	Customer No.:	21559
Title:	METHODS AND COMPOSITIONS FOR THE RAPID AND ENDURING RELIEF OF INADEQUATE MYOCARDIAL INFARCTION		

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' REPLY BRIEF SUBMITTED PURSUANT TO 37 C.F.R. § 1.193(b)

In reply to the Examiner's Answer mailed on August 13, 2003, Appellants submit the following reply brief.

Issues

Appellants acknowledge that three issues are now presented on appeal. The first issue is whether the Examiner erred in rejecting claims 55-60, 62, 63, 65-68, 70, and 71 under 35 U.S.C. § 112, first paragraph as being based on a non-enabling disclosure. The second issue is whether the Examiner erred in rejecting claims 55-71 under 35 U.S.C. § 112, second paragraph as being indefinite. And the third issue is whether the Examiner erred in rejecting claims 55-71 under 35 U.S.C. § 103(a) as being obvious over Sassen et al. (Cardiovasc. Drugs Ther. 1994, 8:179-191; hereafter "Sassen"), Vane et al. (Circulation, 1991; 84:2588-2590; hereafter "Vane"), Lee et al. (Am. J. Cardiol. 1994, 73:1037-1040; hereafter "Lee"), Watts et al. (Lancet 1992, 339:563-569; hereafter "Watts"), and Demopulos et al. (U.S. Patent No. 5,800,385; hereafter "Demopulos").

Grouping of Claims

Appellants maintain that, for the purpose of this appeal, claims 55-60, 62, 63, 65-68, 70, and 71 stand or fall together for the rejection under 35 U.S.C. § 112, first paragraph, and claims 55-71 do not stand or fall together for the rejection under 35 U.S.C. § 103(a). Rather, for the § 103 rejection, claims 55-57, 59-65, and 67-69 stand together, claims 58 and 66 stand together, and claims 70 and 71 stand together for the reasons discussed below. Regarding the rejection under 35 U.S.C. § 112, second paragraph, claims 55-71 also do not stand or fall together. Claims 63 and 64 each stand separately, and claims 55-62 and 65-71 stand together, as discussed below.

Arguments

I. The Present Claims Are Enabled by the Specification

The Examiner has presented no new arguments with regard to the enablement rejection and apparently rests on the argument that Appellants list "[o]nly a few examples" of cholesterol synthesis or transfer inhibitors in the specification. Appellants maintain their position outlined in the Brief on Appeal. In addition, M.P.E.P. § 2164.01 states, "A patent need not teach, and preferably omits, what is well known in the art." (citations omitted). In this regard, as noted in the Brief on Appeal, Appellants have submitted abstracts by Schmidt et al. (*Blood Coagul. Fibrinolysis* 1993, 4:173-175), Yanagita et al. (*Clin. Ther.* 1994, 16:200-208), Bisgaier (*Lipids* 1994, 29:811-818), Chiari et al. (*Pharmacol. Res.* 1996, 33:181-189), and Nicholson et al. (*Lipids* 1995, 30:771-774) to illustrate the use of cholesterol synthesis and transfer inhibitors in the art.

Moreover, Appellants note that the Office bears the burden of proof for a lack of enablement rejection. M.P.E.P. § 2164.04 states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. (emphasis added)

Furthermore, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting

disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439, F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (M.P.E.P. § 2164.04). In the present case, the Examiner has failed to set forth sufficient arguments or evidence to negate the presumption of Appellants' disclosure as enabling. In addition, the Examiner has not commented on the abstracts submitted in support of Appellants' assertion of enablement or provided any rebuttal evidence for these submissions. The § 112, first paragraph rejection should be reversed.

II. The Present Claims Are Definite

The second issue presented on appeal involves the rejection of claims 55-71 for indefiniteness for reciting the language "cholesterol ... transfer inhibitor." In the Answer, the Examiner provides no reason for this rejection, stating only that "[t]he expression 'cholesterol ... transfer inhibitor' in claim 55 renders the claims indefinite as to the compounds encompassed thereby" (Paper 18, page 5).

Appellants reiterate the arguments on definiteness made in the Reply filed on March 5, 2003, which the Examiner did not address. M.P.E.P. § 2173.02 states:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

With regard to the content of the present disclosure, the term "cholesterol transfer inhibitor" is defined as "any compound which retards or blocks the formation of cholesterol ... esters from non-cholesterol sources.... [T]he inhibitor ... may ... act by retarding the action of acetylcholesterol acyl transferase." (pg. 7, ll. 3-7) Thus, a cholesterol transfer inhibitor is any compound that prevents the formation of a cholesterol ester, typically by inhibiting a transferase enzyme. In addition, as stated above, the prior art contains numerous examples of cholesterol transferase inhibitors, and Appellants submitted abstracts from Chiari et al. (*Pharmacol. Res.* 1996, 33:181-189) and Nicholson et al. (*Lipids* 1995, 30:771-774) as evidence of the prior art teachings on these compounds.

One skilled in the art would also understand the meaning of the term "cholesterol transfer inhibitor" as a compound that inhibits a cholesterol transferase based on the prevalent use of similar terminology in the field of medicine. For example, HMG-CoA reductase inhibitors are compounds that inhibit the enzyme HMG-CoA reductase, which the Examiner has noted as being well known in the art (Paper 18, page 10). Appellants have therefore met the conditions for definiteness under M.P.E.P. § 2173.02.

Moreover, Appellants note M.P.E.P. § 2173.01, which states:

> [A]pplicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art. Applicants may use functional language ... which makes clear the boundaries of the subject matter for which protection is sought. (Emphasis added)

In the instant claims, the term "cholesterol transfer inhibitor" is defined in the specification based on its function as an inhibitor of cholesterol esterification. As discussed in the Brief on Appeal, one skilled in the art is a physician who, based on the terminology used in the claims and the description in the specification of the desired outcome, can select an appropriate cholesterol transfer inhibitor from those available. Based on the foregoing arguments, the indefiniteness rejection of claims 55-71 should be reversed.

Moreover, Appellants assert that claims 63 and 64 should be considered separately from each other and from claims 55-62 and 65-71 with respect to the indefiniteness rejection. In claim 63, the cholesterol synthesis or transfer inhibitor is a HMG-CoA reductase inhibitor, and in claim 64, specific, known HMG-CoA reductase inhibitors are recited. With respect to these claims, the Examiner acknowledges that, "HMG-CoA reductase inhibitors ... [are] well known to be cholesterol synthesis inhibitors." (Paper 18, page 10). Since, as the Examiner has noted, these terms are well known in the art, the skilled artisan would understand the metes and bounds of these claims, and the rejection for indefiniteness with respect to claims 63 and 64 should be reversed.

III. Appellants' Claimed Method Is Not Suggested by the Prior Art

As stated in the Brief on Appeal, the Office must put forth a *prima facie* case that meets the legal standard for obviousness found in M.P.E.P. § 2142 to

support an obviousness rejection. This standard requires some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; a reasonable expectation of success; and a teaching or suggestion of all the claim limitations in the prior art reference (or references when combined). Appellants surveyed the relevant standards established by the Federal Circuit in the Brief on Appeal.

In applying these legal standards to the present case, the Office has still failed to established a *prima facie* case of obviousness after the Examiner's Answer. Claim 55, from which all other claims depend, recites:

> 55. A method for reducing coronary artery stenosis by at least 20% in a mammal comprising the administration to said mammal of a combination of (a) a composition comprising eicosapentaeneoic acid or docosahexaeneoic acid and (b) a cholesterol synthesis or transfer inhibitor, in combination with limiting fat or cholesterol intake, whereby a serum LDL concentration of less than or equal to 70 mg/dl is achieved. (emphasis added)

Thus, the present claims are all directed to methods for reducing established narrowing in coronary arteries using a combination therapy requiring three components: (1) eicosapentaeneoic acid or docosahexaeneoic acid (components of fish oil), (2) a cholesterol synthesis or transfer inhibitor, and (3) limiting fat or cholesterol intake. Claims 58 and 66 further include the administration of aspirin, and claims 70 and 71 further include the administration of buspirone, as components of the method of claim 55.

In review, the Office has cited four references to support the obviousness rejection, Sassen (Cardiovasc. Drugs Ther. 1994, 8:179-191), Lee (Am. J. Cardiol. 1994, 73:1037-1040), Vane (Circulation, 1991; 84:2588-2590), and Watts (Lancet 1992, 339:563-569) as teaching the three major components of the claimed methods, with Demopulos (U.S. Patent No. 5,800,385) cited as teaching an additional element in claim 70. Sassen reviews several studies on the use of fish oil for the prevention and regression of atherosclerosis. Vane discloses the use of aspirin and fish oil for the prevention of thrombosis. Lee discloses the use of pravastatin, niacin, and LDL apheresis for the prevention of restenosis after angioplasty. Watts teaches the use of a controlled diet, with or without administration of cholestyramine, for the regression of atherosclerosis. And Demopulos teaches the use of a solution of various compounds, potentially including buspirone, to inhibit undesirable effects (e.g., pain, inflammation, spasm, and restenosis) of cardiovascular therapeutic and diagnostic procedures.

Appellants discuss the issues raised in the Answer regarding the § 103 rejection in more detail below.

A. The References Do Not Teach or Suggest All of the Claim Limitations

As stated above, claim 55 and its dependent claims are directed to methods of reducing coronary artery stenosis by 20% by treatment with eicosapentaeneoic acid or docosahexaeneoic acid, a cholesterol synthesis or transfer inhibitor, and limited fat or cholesterol intake. Appellants argued in the Brief on Appeal that the instantly cited

references do not teach or suggest all of the elements of the instant claims because the claims are directed to methods of reducing stenosis, while certain prior art references disclose only prevention or reduction of the extent of restenosis. In reply to these arguments, the Examiner states:

> [T]he expression reduction of stenosis (narrowing of the arteries) actually encompasses any degree of reduction of narrowing of coronary arteries, wherein the narrowing can be caused by any etiologies. Thus, prevention (100% of reduction) or [sic] stenosis recurrence after angioplasty (etiology of lumen proliferation) is still read on the instant claims. (Paper 18, pages 10-11) (emphasis in original)

This statement is simply incorrect. First, the claims do not encompass "any degree of reduction" of stenosis because they are limited to reducing stenosis by 20% or more. In addition, the Examiner's continued reliance on an equivalence between prevention and reduction is erroneous. The Examiner likely persists in this view because it is necessary to justify the combinations of references that are used to reject the instant claims.

Despite the Examiner's assertion, prevention is not 100% reduction. The plain meaning of "reducing stenosis" is the act of diminishing the extent of a narrowing in a coronary artery. Reducing stenosis therefore necessarily results in an increase in the diameter of a coronary artery. In contrast, "preventing stenosis" is the act of keeping a narrowing in a coronary artery from existing. Preventing stenosis therefore necessarily results in no change in the diameter of a coronary artery. Prevention and reduction are two separate phenomena.

In addition, the ability to prevent deposition of a substance on a surface does not imply the ability to reduce the amount of that substance once deposited. In this regard, the Examiner has provided no documentary evidence that compounds showing some efficacy in preventing restenosis are effective in reducing the amount of coronary narrowing, i.e., increasing the diameter of a coronary artery, to any extent, much less the 20% or more required by the instant claims. Thus, the fact that a particular therapeutic agent was employed to treat restenosis standing alone is irrelevant to the patentability of the same agent employed in the present methods.

As stated in the Brief of Appeal, the Office has cited only one reference, Lee, as disclosing the use of a cholesterol synthesis or transfer inhibitor – the compound pravastatin. Lee, however, only discusses the use of pravastatin as one component of a treatment for the prevention of restenosis. Lee fails entirely to disclose that pravastatin is useful for the reduction of stenosis in patients already having occluded coronary arteries. No other reference has been cited for this proposition. Thus, the Office has failed to provide a teaching of one of the three major components of the methods of the instant claims for the reduction of stenosis, and, on this basis alone, the rejection should be reversed.

B. There Is No Motivation to Combine the References

In addition to the above deficiencies in the cited references, there also exists no motivation for their combination. The only basis put forth for this combination currently

made of record remains the assertion by the Office, based on *In re Kerkhoven*, 625 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (M.P.E.P. § 2144.06) that "it flows logically to combine or incorporate agents, which are known to be useful individually for treating or preventing restenosis, into a single combination or method useful for the same purpose." (Paper 18, page 11) (emphasis added).

Appellants maintain that Sassen provides no motivation for the use of fish oil in a method for reducing stenosis. In response to these arguments, the Examiner states that "in page 187, Sassen listed four studies on the effectiveness of fish oil in regression of atherosclerotic lesions and later concludes that fish oil is effective in leading [to] regression in certain kinds or components of atherosclerotic lesions." (Paper 18, page 11). Appellants disagree. While Sassen does discuss four studies on the use of fish oil in the regression of atherosclerosis, these studies are inconclusive: one study in swine and one in rabbits showed regression, another in swine showed no regression, and a study in green monkeys (the animal model closest to humans) actually showed worsening of atherosclerotic plaque. Indeed, Sassen states, "The number of animal studies investigating the effects of fish oil on the regression of atherosclerosis is too small to draw any conclusion..." (page 188, col. 1). Thus, in contrast to the Examiner's assertion, Sassen never concludes that fish oil is effective in reducing stenosis.

Furthermore, Appellants previously noted that Sassen questions the underlying motivation for studying medical uses of fish oil. In the Answer, the Examiner states, "The passage in Sassen [on page 188, relied upon by Appellants,] merely teaches that

other factors would have also played a role in [atherosclerotic plaque] development." (Paper 18, page 11). This statement is simply incorrect. While Sassen does discuss several factors for the development of atherosclerosis, it is clearly from the point of view of factors other than and not in addition to consumption of fish oil. For example, Sassen states that "[i]t is thus quite feasible that genetic factors may prove to be more vital than dietary regimen ... [and] [i]t has also been questioned if the abstinence from meat from mammals living on land rather than the consumption of fish can cause difference in the incidence in ischemic heart disease." (page 188, col. 1) (emphasis added). Based on the teachings of Sassen as a whole, there is no motivation to employ fish oil in a method for reducing stenosis.

Regarding Watts, the Examiner states that "controlled diet plus [c]holesterol-lowering agent is clearly superior to controlled diet alone." (Paper 18, page 12) Watts, however, actually "found diet plus cholestyramine to be more effective than diet alone, except in patients with >50% stenosis at outset..." (page 568, col. 1) (emphasis added) As shown in Table V, only the group with >50% stenosis at outset that received controlled diet alone experienced a greater than 20% reduction in stenosis. In contrast, a similar group treated with a combination of diet and cholestyramine did not achieve a 20% reduction in stenosis. Thus, Watts teaches away from the use of a combination of controlled diet and cholestyramine for reducing stenosis by greater than 20%, since the combination failed to achieve that result. The data on which the Examiner relies are for much lower levels of reduction, typically around 1%, on average. Since these levels of

reduction are significantly lower than the 20% required by claim 55, they do not support the Examiner's position. This is further emphasized by Watts' teachings that the combination of diet and cholestyramine, as compared to diet alone, is less efficacious in reducing stenosis, leading one reading these references away from Appellants' claimed technique.

In view of the above, Appellants again submit that the references fail to provide the necessary motivation for their combination, and the Office has therefore failed to establish a *prima facie case* of obviousness for claim 55 and its dependent claims. On this basis as well, the rejection of Appellants' claims for obviousness should be reversed.

C. The Prior Art Provides No Reasonable Expectation of Success

Appellants maintain that the instant claims are directed to methods for reducing coronary artery stenosis by at least 20%, and none of the cited references suggests that such a reduction is possible using the instantly claimed method.

In the Answer, the Examiner states that Watts teaches that the combination of diet and a cholesterol-lowering drug is superior to diet alone. As discussed above, while Watts teaches a 23.3% reduction in stenosis in limited cases using diet alone, this outcome was lessened in similar cases when diet was combined with a cholesterol-lowering drug. The Examiner has not rebutted this position, and Watts provides no reasonable expectation for a 20% reduction in stenosis for a method that includes both a controlled diet and cholesterol-lowering drug, as instantly claimed.

The Office asserts that "Sassen, as a whole, teaches the benefit of fish oil on treating and/or preventing [atherosclerosis]." (Paper 18, page 13). The Examiner addressed Appellants' arguments on Sassen by singling out only two of the four studies on regression of atherosclerosis in animals to support his position (Paper 18, pages 12-13). As stated above, Sassen disclosed two animal studies showing regression, one showing no change, and one showing worsening of the disease state. Appellants further note that the two studies in swine did not achieve the same results. Based on these studies, Sassen, and thus one skilled in the art, could not draw any conclusions on the effectiveness of fish oil in reducing stenosis (page 188). Since Sassen provides no other teachings on the reduction of stenosis, Sassen as a whole cannot teach the benefits of fish oil for that purpose.

The Examiner also relies on statements in Sassen that are not directed to the reduction of stenosis. For example, the Examiner states, "Sassen et al. also disclosed that [atherosclerosis] is a multi-factorial disease and it is apparent that in model[s] wherein platelet aggregation is the dominant cause, fish oil is effective." (Paper 18, page 13). While Sassen does make this statement (pg. 187, col. 2), it is with regard to <u>preventing</u> progression of atherosclerosis (pg. 185, col. 2) and not <u>reducing</u> atherosclerosis as required in the instant claims. Sassen therefore fails to provide any reasonable expectation that a treatment for reducing stenosis that included fish oil would be effective at all, much less induce a 20% reduction, as required by claim 55.

In sum, Appellants maintain that nowhere in the cited references is a *prima facie* case of obviousness for the methods of instant claim 55 and its dependent claims established. The references, while providing a list of therapeutics and behavioral modifications, do not teach the unique combinations of claims 55-71, nor do they provide a motivation to combine the references or a reasonable expectation of their success. The § 103 rejection of claims 55-71 should be reversed.

D. Claims 58, 66, 70, and 71

In the Answer, the Examiner disagrees with Appellants' grouping of claims for the § 103 rejection because "the various groups differ by employing three different agents: niacin, aspirin, and buspirone." (Paper 18, page 2) (emphasis added). The only other support for this position is the general statement that "[t]he groups are not independent as to patentability and separately patentable over the art of record." (Paper 18, pages 2-3). While claims 58 and 66 recite methods employing aspirin, and claims 70 and 71 recite methods employing buspirone, only claims 57 and 65 in the group of claims 55-57, 59-65, and 67-69 recite methods employing niacin.

Appellants again assert that the three groups identified for the § 103 rejection are separately patentable, precisely for the reason the Examiner concludes that they are not – the groups recite the use of different agents. General teachings regarding aspirin are only provided by Vane, and general teachings regarding buspirone are only provided by Demopulos. A group whose rejection relies on Demopulos but not Vane and a group

whose rejection relies on Vane but not Demopulos are separately patentable from each other and from a group whose rejection relies on neither Demopulos nor Vane. Thus, claims 58 and 66 and claims 70-71 should stand separately from claims 55-57, 59-65, and 67-69 for the purposes of this appeal.

Claims 58 and 66 are directed to the method of reducing stenosis of claim 55 further including the administration of aspirin. Regarding claims 58 and 66 in the Answer, the Examiner has merely repeated its previous arguments, again without citing any documentary evidence as requested by Appellants and required under M.P.E.P. § 2144.03(c).

In reply to Appellants' arguments regarding claims 70-71, the Examiner states that "Appellant's [sic] arguments averring the teaching of Demopulos ... apparently rely on the concept of reducing stenosis not being equal to treatment of restenosis." (Paper 18, page 14). This statement is incorrect. While Appellants do state that the teachings of Demopulos as related to the use of compounds for the treatment of restenosis are irrelevant to the patentability of a method of reducing stenosis, Appellants also note that Demopulos does not teach that buspirone is useful for prevention of restenosis. Thus, assuming arguendo that treating of restenosis and reducing stenosis are equivalent (which they are not), Demopulos still does not teach what is asserted by the Office. Instead, Demopulos teaches that buspirone is used for the treatment of inflammation and pain (col. 9, ll. 8-10 and col. 13, ll. 1-10), and not for stenosis or even restenosis.

Furthermore, the Examiner has ignored Appellants' arguments regarding the motivation to combine Demopluos with the other cited references. Regarding motivation, Demopulos teaches that buspirone is an anti-inflammation/anti-pain agent and is silent with regard to treatments for reducing stenosis. Thus, Demopulos fails to teach that buspirone is appropriate for the treatment of Appellants' coronary disease. In addition, Demopulos also discloses numerous agents for treatment of various conditions, and the Office has failed to indicate why one skilled in the art would select buspirone from these agents for inclusion in any method, much less a method of reducing stenosis. As held by the Federal Circuit, "there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant" (emphasis added). *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). Based on this standard, there is no motivation of record to support a *prima facie* case of obviousness for claims 70 or 71.

Conclusion

Appellants again respectfully request that the rejection of claims 55-71 be reversed. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 14 October 2003

Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045